1. NAME OF THE MEDICINAL PRODUCT

Singulair 4 mg chewable tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One chewable tablet contains montelukast sodium, which is equivalent to 4 mg montelukast.

Excipients with known effect: This medicine contains 1.2 mg aspartame (E 951) per tablet.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.

Pink, oval, biconvex-shaped tablets, SINGULAIR engraved on one side and MSD 711 on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Singulair is indicated in the treatment of asthma as add-on therapy in those 2 to 5 year old patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom "as-needed" short acting β-agonists provide inadequate clinical control of asthma.
Singulair may also be an alternative treatment option to low-dose inhaled corticosteroids for 2 to 5 year old patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids.
Singulair is also indicated in the prophylaxis of asthma from 2 years of age and older in which the predominant component is exercise-induced bronchoconstriction.

4.2 Posology and method of administration

This medicinal product is to be given to a child under adult supervision.
The dosage for paediatric patients 2-5 years of age is one 4 mg chewable tablet daily to be taken in the evening. If taken in connection with food, Singulair should be taken 1 hour before or 2 hours after food. No dosage adjustment within this age group is necessary. The Singulair 4 mg chewable tablet formulation is not recommended below 2 years of age.
General recommendations. The therapeutic effect of Singulair on parameters of asthma control occurs within one day. Patients should be advised to continue taking Singulair even if their asthma is under control, as well as during periods of worsening asthma.
No dosage adjustment is necessary for patients with renal insufficiency, or mild to moderate hepatic impairment. There are no data on patients with severe hepatic impairment. The dosage is the same for both male and female patients.
Singulair *as an alternative treatment option to low-dose inhaled corticosteroids for mild, persistent asthma*: Montelukast is not recommended as monotherapy in patients with

moderate persistent asthma. The use of montelukast as an alternative treatment option to low-dose inhaled corticosteroids for children with mild persistent asthma should only be considered for patients who do not have a recent history of serious asthma attacks that required oral corticosteroid use and who have demonstrated that they are not capable of using inhaled corticosteroids. Mild persistent asthma is defined as asthma symptoms more than once a week but less that once a day, nocturnal symptoms more than twice a month but less than once a week, normal lung function between episodes. If satisfactory control of asthma is not achieved at follow-up (usually within one month), the need for an additional or different anti-inflammatory therapy based on the step system for asthma therapy should be evaluated. Patients should be periodically evaluated for their asthma control.
Singulair *as prophylaxis of asthma for 2 to 5 year old patients in whom the predominant component is exercise-induced bronchoconstriction:* In 2 to 5 year old patients, exercise-induced bronchoconstriction may be the predominant manifestation of persistent asthma that requires treatment with inhaled corticosteroids. Patients should be evaluated after 2 to 4 weeks of treatment with montelukast. If satisfactory response is not achieved, an additional or different therapy should be considered.
Therapy with Singulair *in relation to other treatments for asthma.*
When treatment with Singulair is used as add-on therapy to inhaled corticosteroids, Singulair should not be abruptly substituted for inhaled corticosteroids
4-mg chewable tablets are available for paediatric patients 2 to 5 years of age.
Do not give Singulair 4 mg chewable tablets to children less than 2 years of age. The safety and efficacy of Singulair 4 mg chewable tablets in children less than 2 years of age has not been established.
5 mg chewable tablets are available for paediatric patients 6 to 14 years of age.
In the case of a missed dose, patients should be advised to take the next dose at the regular time. Patients should not take 2 doses at the same time.
Method of administration
Oral use.
The tablets are to be chewed before swallowing.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Patients and/or caregivers should be advised never to use oral montelukast to treat acute asthma attacks and to keep their usual appropriate rescue medication for this purpose readily available. If an acute attack occurs, a short-acting inhaled β-agonist should be used. Patients should seek their doctors' advice as soon as possible if they need more inhalations of short-acting β-agonists than usual.
Montelukast should not be abruptly substituted for inhaled or oral corticosteroids.
There are no data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly.
In rare cases, patients on therapy with anti-asthma agents including montelukast may present with
systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These cases usually, but not always have been associated with the reduction or withdrawal of oral corticosteroid therapy. the possibility that leukotriene receptor antagonists may be associated with the emergence of Charg-Strauss syndrome can neither be excluded nor established physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients.

Patients who develop these symptoms should be reassessed and their treatment regimens evaluated.
Treatment with montelukast does not alter the need for patients with aspirin-sensitive asthma to avoid taking aspirin and other non-steroidal anti-inflammatory drugs.
Neuropsychiatric events have been reported in adults, adolescents, and children taking Singulair (see section a4.8). Patients and physicians should be alert for neuropsychiatric events. Patients and/or caregivers should be instructed to notify their physician if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with Singulair if such events occur.
Singulair contains aspartame, a source of phenylalanine. Patients with phenylketonuria should take into account that each 4 mg chewable tablet contains phenylalanine in an amount equivalent to 0.674 mg phenylalanine per dose.
This medicinal product is essentially "sodium-free" (i.e., contains less than 23 mg sodium per dose).

4.5 Interactions with other medicinal products and other forms of interaction

Montelukast may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following medicinal products: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.
The area under the plasma concentration curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. Since montelukast is metabolised by CYP 3A4, 2C8 and 2C9 caution should be exercised, particularly in children, when montelukast is coadministered with inducers of CYP 3A4, 2C8 and 2C9, such as phenytoin, phenobarbital and rifampicin.
In vitro studies have shown that montelukast is a potent inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of medicinal products primarily metabolized by CYP 2C8) demonstrated that montelukast does not inhibit CYP 2C8 in vivo. Therefore, montelukast is not anticipated to markedly alter the metabolism of medicinal products metabolized by this enzyme (e.g., paclitaxel, rosiglitazone, and repaglinide.)
In vitro studies have shown that montelukast is a substrate of CYP 2C8, and to a less significant extent, of 2C9, and 3A4. In a clinical drug drug interaction study involving montelukast and gemfibrozil (an inhibitor of both CYP 2C8 and 2C9) gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. No routine dosage adjustment of montelukast is required upon co-administration with gemfibrozil or other potent inhibitors of CYP 2C8, but the physician should be aware of the potential for an increase in adverse reactions.
Based on in vitro data, clinically important drug interactions with less potent inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. Co-administration of montelukast with itraconazole, a strong inhibitor of CYP 3A4, resulted in no significant increase in the systemic exposure of montelukast.

4.6 Fertility, pregnancy and lactation

Use during pregnancy.
Human Data
Carcinogenicity:
Montelukast sodium was not carcinogenic when administered at oral doses of up to 200 mg/kg/day in a 106-week study in rats, or at oral doses of up to 100 mg/kg/day in a 92-week study in mice. These doses are equivalent to 1000 times and 500 times the recommended

adult human dose*.

Reproduction:
Fertility and reproductive performance were not affected in studies with male rats given oral doses of up to 800 mg/kg/day or with female rats given doses of up to 100 mg/kg/day. These dosages provide margins of 4000-fold and 500-fold, respectively, above the recommended adult human dose*.
Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a drug-associated risk. Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups.

Pregnancy:
Singulair may be used during pregnancy only if it is considered to be clearly essential. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Breastfeeding:
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Singulair and any potential adverse effects on the breastfed infant from Singulair or from the underlying maternal condition.
Singulair may be used in breast-feeding mothers only if it is considered to be clearly essential.

Animal Data
Animal studies do not indicate harmful effects with respect to effects on pregnancy or embryonal/foetal development. Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk.

4.7 Effects on ability to drive and use machines

Montelukast is not expected to affect a patient's ability to drive a car or operate machinery. However, in very rare cases, individuals have reported drowsiness or dizziness.

4.8 Undesirable effects

Montelukast has been evaluated in clinical studies in patients with persistent asthma as follows:
• 10 mg film-coated tablets in approximately 4000 adult patients 15 years of age and older
• 5 mg chewable tablets in approximately 1750 paediatric patients 6 to 14 years of age, and
• 4 mg chewable tablets in 851 paediatric patients 2 to 5 years of age.
Montelukast has been evaluated in a clinical study in patients with intermittent asthma as follows:
• 4 mg granules and chewable tablets in 1038 paediatric patients 6 months to 5 years of age
The following drug-related adverse reactions in clinical studies were reported commonly (≥1/100 to <1/10) in patients treated with montelukast and at a greater incidence than in patients treated with placebo:

Body System Class	Adult Patients 15 years and older (two 12-week studies; n=795)	Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56 week studies; n=615)	Paediatric Patients 2 to 5 years old (one 12-week study; n=461) (one 48-week study; n=278)

Nervous system disorders	Headache	headache	
Gastrointestinal disorders	abdominal pain		abdominal pain
General disorders and administration site conditions			thirst

With prolonged treatment in clinical trials with a limited number of patients for up to 2 years for adults, and up to 12 months for paediatric patients 6 to 14 years of age, the safety profile did not change.
Cumulatively, 502 paediatric patients 2 to 5 years of age were treated with montelukast for at least 3 months, 338 for 6 months or longer, and 534 patients for 12 months or longer. With prolonged treatment, the safety profile did not change in these patients either.
Post-marketing Experience
Adverse reactions reported in post-marketing use are listed, by System Organ Class and specific Adverse Experience Term, in the table below. Frequency Categories were estimated based on relevant clinical trials.
Infections and infestations: very common - upper respiratory infection.
Blood and lymphatic system disorders: rare - increased bleeding tendency, thrombocytopenia.
Immune system disorders: uncommon - hypersensitivity reactions including anaphylaxis, very rare – hepatic eosinophilic infiltration.
Psychiatric disorders: uncommon - dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor§); rare – disturbance in attention, memory impairment, obsessive-compulsive symptoms; very rare - hallucinations, dysphemia (stuttering), disorientation, suicidal thinking and behaviour (suicidality), tic.
Nervous system disorders: uncommon - dizziness drowsiness, paraesthesia/hypoesthesia, seizure.
Cardiac disorders: rare - palpitations.
Respiratory, thoracic and mediastinal disorders: uncommon – epistaxis; very rare - Churg-Strauss Syndrome, pulmonary eosinophilia.
Gastrointestinal disorders: common - diarrhea, nausea, vomiting; uncommon - dry mouth, dyspepsia.
Hepatobiliary disorders: common - elevated levels of serum transaminases (ALT, AST); very rare - hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).
Skin and subcutaneous tissue disorders: common – rash; uncommon – bruising, urticaria, pruritus, rare – angioedema; very rare - erythema nodosum, erythema multiforme.
Musculoskeletal and connective tissue disorders: uncommon – arthralgia, myalgia including muscle cramps.
Renal and urinary disorders: enuresis in children
General disorders and administration site conditions: common – pyrexia; uncommon - asthenia/fatigue, malaise, oedema.
§ Frequency Rare

If the patient experiences any of these adverse reactions, or any other adverse reactions not specified in this PI, the patient should consult their doctor.

4.9 Overdose

No specific information is available on the treatment of overdose with montelukast. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and in short term studies, up to 900 mg/day to patients for approximately one

week without clinically important adverse experiences.
There have been reports of acute overdose in post-marketing experience and clinical studies with montelukast. These include reports in adults and children with a dose as high as 1000 mg (approximately 61 mg/kg in a 42 month old child). The clinical and laboratory findings observed were consistent with the safety profile in adults and paediatric patients. There were no adverse experiences in the majority of overdose reports. The most frequently occurring adverse experiences were consistent with the safety profile of montelukast and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.
In the event of overdose, it is reasonable to employ the usual supportive measures e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required. It is not known whether montelukast is dialyzable by peritoneal- or hemo-dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other systemic drugs for obstructive airway diseases, leukotriene receptor antagonist.

ATC-code: R03D C03

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene receptors (CysLT) found in the human airway and cause airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.
Montelukast is an orally active compound which binds with high affinity and selectivity to the $CysLT_1$ receptor. In clinical studies, montelukast inhibits bronchoconstriction due to inhaled LTD_4 at doses as low as 5 mg. Bronchodilation was observed within 2 hours of oral administration. The bronchodilation effect caused by a β-agonist was additive to that caused by montelukast. Treatment with montelukast inhibited both early- and late-phase bronchoconstriction due to antigen challenge. Montelukast, compared with placebo, decreased peripheral blood eosinophils in adult and paediatric patients. In a separate study, treatment with montelukast significantly decreased eosinophils in the airways (as measured in sputum). In adult and paediatric patients 2 to 14 years of age, montelukast, compared with placebo, decreased peripheral blood eosinophils while improving clinical asthma control.
In studies in adults, montelukast, 10 mg once daily, compared with placebo, demonstrated significant improvements in morning FEV_1 (10.4% vs 2.7% change from baseline), AM peak expiratory flow rate (PEFR) (24.5 L/min vs 3.3 L/min change from baseline), and significant decrease in total β-agonist use (-26.1% vs -4.6% change from baseline). Improvement in patient-reported daytime and nighttime asthma symptoms scores was significantly better than placebo.
Studies in adults demonstrated the ability of montelukast to add to the clinical effect of inhaled corticosteroid (% change from baseline for inhaled beclomethasone plus montelukast vs beclomethasone, respectively for FEV_1: 5.43% vs 1.04%; β-agonist use: -8.70% vs 2.64%). Compared with inhaled beclomethasone (200 µg twice daily with a spacer device), montelukast demonstrated a more rapid initial response, although over the 12-week study, beclomethasone provided a greater average treatment effect (% change from baseline for montelukast vs beclomethasone, respectively for FEV_1: 7.49% vs 13.3%; β-agonist use: -28.28% vs -43.89%). However, compared with beclomethasone, a high percentage of patients treated with montelukast achieved similar clinical responses (e.g., 50% of patients treated

with beclomethasone achieved an improvement in FEV_1 of approximately 11% or more over baseline while approximately 42% of patients treated with montelukast achieved the same response).
In a 12-week, placebo-controlled study in paediatric patients 2 to 5 years of age, montelukast 4 mg once daily improved parameters of asthma control compared with placebo irrespective of concomitant controller therapy (inhaled/nebulized corticosteroids or inhaled/nebulized sodium cromoglycate). Sixty percent of patients were not on any other controller therapy. Montelukast improved daytime symptoms (including coughing, wheezing, trouble breathing and activity limitation) and nighttime symptoms compared with placebo. Montelukast also decreased "as-needed" β-agonist use and corticosteroid rescue for worsening asthma compared with placebo. Patients receiving montelukast had more days without asthma than those receiving placebo. A treatment effect was achieved after the first dose.
In a 12-month, placebo-controlled study in paediatric patients 2 to 5 years of age with mild asthma and episodic exacerbations, montelukast 4 mg once daily significantly ($p \leq 0.001$) reduced the yearly rate of asthma exacerbation episodes (EE) compared with placebo (1.60 EE vs. 2.34 EE, respectively), [EE defined as ≥3 consecutive days with daytime symptoms requiring β-agonist use, or corticosteroids (oral or inhaled), or hospitalization for asthma]. The percentage reduction in yearly EE rate was 31.9%, with a 95% CI of 16.9, 44.1.
In a placebo-controlled study in paediatric patients 6 months to 5 years of age who had intermittent asthma but did not have persistent asthma, treatment with montelukast was administered over a 12-month period, either as a once-daily 4 mg regimen or as a series of 12-day courses that each were started when an episode of intermittent symptoms began. No significant difference was observed between patients treated with montelukast 4 mg or placebo in the number of asthma episodes culminating in an asthma attack, defined as an asthma episode requiring utilization of health-care resources such as an unscheduled visit to a doctor's office, emergency room, or hospital; or treatment with oral, intravenous, or intramuscular corticosteroid.
In an 8-week study in paediatric patients 6 to 14 years of age, montelukast 5 mg once daily, compared with placebo, significantly improved respiratory function (FEV_1 8.71% vs 4.16% change from baseline; AM PEFR 27.9 L/min vs 17.8 L/min change from baseline) and decreased "as-needed" β-agonist use (-11.7% vs +8.2% change from baseline).
In a 12-month study comparing the efficacy of montelukast to inhaled fluticasone on asthma control in paediatric patients 6 to 14 years of age with mild persistent asthma, montelukast was non-inferior to fluticasone in increasing the percentage of asthma rescue-free days (RFDs), the primary endpoint. Averaged over the 12-month treatment period, the percentage of asthma RFDs increased from 61.6 to 84.0 in the montelukast group and from 60.9 to 86.7 in the fluticasone group. The between group difference in LS mean increase in the percentage of asthma RFDs was statistically significant (-2.8 with a 95% CI of -4.7, -0.9), but within the limit pre-defined to be clinically not inferior.
Both montelukast and fluticasone also improved asthma control on secondary variables assessed over the 12 month treatment period:
FEV_1 increased from 1.83 L to 2.09 L in the montelukast group and from 1.85 L to 2.14 L in the fluticasone group. The between-group difference in LS mean increase in FEV_1 was -0.02 L with a 95% CI of -0.06, 0.02. The mean increase from baseline in % predicted FEV_1 was 0.6% in the montelukast treatment group, and 2.7% in the fluticasone treatment group. The difference in LS means for the change from baseline in the % predicted FEV_1 was significant: -2.2% with a 95% CI of -3.6, -0.7.
The percentage of days with β-agonist use decreased from 38.0 to 15.4 in the montelukast group, and from 38.5 to 12.8 in the fluticasone group. The between group difference in LS means for the percentage of days with β-agonist use was significant: 2.7 with a 95% CI of 0.9, 4.5.
The percentage of patients with an asthma attack (an asthma attack being defined as a period

of worsening asthma that required treatment with oral steroids, an unscheduled visit to the doctor's office, an emergency room visit, or hospitalization) was 32.2 in the montelukast group and 25.6 in the fluticasone group; the odds ratio (95% CI) being significant: equal to 1.38 (1.04, 1.84).
The percentage of patients with systemic (mainly oral) corticosteroid use during the study period was 17.8% in the montelukast group and 10.5% in the fluticasone group. The between group difference in LS means was significant: 7.3% with a 95%CI of 2.9; 11.7.
Significant reduction of exercise-induced bronchoconstriction (EIB) was demonstrated in a 12-week study in adults (maximal fall in FEV_1 22.33% for montelukast vs 32.40% for placebo; time to recovery to within 5% of baseline FEV_1 44.22 min vs 60.64 min). This effect was consistent throughout the 12-week study period. Reduction in EIB was also demonstrated in a short term study in paediatric patients 6 to 14 years of age (maximal fall in FEV_1 18.27% vs 26.11%; time to recovery to within 5% of baseline FEV_1 17.76 min vs 27.98 min). The effect in both studies was demonstrated at the end of the once-daily dosing interval.
In aspirin-sensitive asthmatic patients receiving concomitant inhaled and/or oral corticosteroids, treatment with montelukast, compared with placebo, resulted in significant improvement in asthma control (FEV_1 8.55% vs -1.74% change from baseline and decrease in total β-agonist use -27.78% vs 2.09% change from baseline).

5.2 Pharmacokinetic properties

Absorption
Montelukast is rapidly absorbed following oral administration. For the 10 mg film-coated tablet, the mean peak plasma concentration (C_{max}) is achieved 3 hours (T_{max}) after administration in adults in the fasted state. The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal.

After administration of the 4 mg chewable tablet to paediatric patients 2 to 5 years of age in the fasted state, C_{max} is achieved 2 hours after administration. The mean C_{max} is 66% higher while mean C_{min} is lower than in adults receiving a 10 mg tablet.
For the 4-mg chewable tablet, C_{max} is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.
Safety and efficacy were demonstrated in clinical studies where the 4-mg chewable tablet, 5-mg chewable tablet and 10 mg film-coated tablet were administered without regard to the timing of food ingestion.
Distribution
Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8-11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours post-dose were minimal in all other tissues.
Metabolism
Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and children.
In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2A6, 2 C8 and 2C9 are involved in the metabolism of montelukast. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. The contribution of metabolites to the therapeutic effect of montelukast is minimal.
Elimination
The plasma clearance of montelukast averages 45 ml/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral

bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.
In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. No difference in pharmacokinetics was noted between dosing in the morning or in the evening. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (~14%).

Characteristics in patients

No dosage adjustment is necessary for the elderly or mild to moderate hepatic insufficiency. Studies in patients with renal impairment have not been undertaken. Because montelukast and its metabolites are eliminated by the biliary route, no dose adjustment is anticipated to be necessary in patients with renal impairment. There are no data on the pharmacokinetics of montelukast in patients with severe hepatic insufficiency (Child-Pugh score>9).
With high doses of montelukast (20- and 60-fold the recommended adult dose), a decrease in plasma theophylline concentration was observed. This effect was not seen at the recommended dose of 10 mg once daily.
Pharmacokinetic studies show that the plasma profiles of the 4-mg chewable tablet in pediatric patients 2 to 5 years of age and the 5-mg chewable tablets in pediatric patients 6 to 14 years of age were similar to the plasma profile of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age and the 4-mg chewable tablet in pediatric patients 2 to 5 years of age.

5.3 Preclinical safety data

In animal toxicity studies, minor serum biochemical alterations in ALT, glucose, phosphorus and triglycerides were observed which were transient in nature. The signs of toxicity in animals were increased excretion of saliva, gastrointestinal symptoms, loose stools and ion imbalance. These occurred at dosages which provided >17-fold the systemic exposure seen at the clinical dosage. In monkeys, the adverse effects appeared at doses from 150 mg/kg/day (>232-fold the systemic exposure seen at the clinical dose). In animal studies, montelukast did not affect fertility or reproductive performance at systemic exposure exceeding the clinical systemic exposure by greater than 24-fold. A slight decrease in pup body weight was noted in the female fertility study in rats at 200 mg/kg/day (>69-fold the clinical systemic exposure). In studies in rabbits, a higher incidence of incomplete ossification, compared with concurrent control animals, was seen at systemic exposure >24-fold the clinical systemic exposure seen at the clinical dose. No abnormalities were seen in rats. Montelukast has been shown to cross the placental barrier and is excreted in breast milk of animals.

No deaths occurred following a single oral administration of montelukast sodium at doses up to 5,000 mg/kg in mice and rats (15,000 mg/m^2 and 30,000 mg/m^2 in mice and rats, respectively), the maximum dose tested. This dose is equivalent to 25,000 times the recommended daily adult human dose (based on an adult patient weight of 50 kg).

Montelukast was determined not to be phototoxic in mice for UVA, UVB or visible light spectra at doses up to 500 mg/kg/day (approximately >200-fold based on systemic exposure).

Montelukast was neither mutagenic in *in vitro* and *in vivo* tests nor tumorigenic in rodent species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose
hydroxypropyl cellulose

Red ferric oxide
Croscarmellose sodium
Cherry flavour
Aspartame
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years. Do not use after expiry date.

6.4 Special precautions for storage

Store below 30ºC. Store in the original package in order to protect from light and moisture. Keep away from children.

6.5 Nature and contents of container

14 chewable tablets of 4 mg in the blister.
1 or 2 blisters and instruction for medical use of the drug in carton box.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Organon Central East GmbH, Weystrasse 20, 6006 Luzern, Switzerland

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]